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CONSTRUCTION AND VALIDATION OF A PHARMACOGENETIC REFINEMENT ALGORITHM FOR THE ESTIMATION OF THE WARFARIN DOSE IN CHINESE PATIENTS

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Objectives Pharmacogenetic refinement algorithm on the basis of early international normalised ratio (INR), clinical factors, and genotypes is promising for the accurate prediction of warfarin dose. However, it has never been constructed in Chinese patients. In this study, we aimed to develop and validate a pharmacogenetic refinement algorithm for the estimation of warfarin dose in Chinese patients.

Methods A total of 310 Chinese-Han patients under stable warfarin treatment were recruited prospectively, and divided randomly into derivation (n=207) and validation cohort (n=103). Genomic DNA extraction for each patients was followed by the genotyping of three genetic variations (CYP2C9*3, VKORC1-1639A/G, and CYP4F2 rs2108622) with the method of SEQUENOM. Clinical and genetic data together with INR value on day 4 of therapy from the patients in the derivation cohort were used to create a pharmacogenetic refinement algorithm. In the validation cohort, the predictive accuracy of the refinement algorithm, and the performance compared with the clinical algorithm and the pharmacogenetic algorithm developed by the International Warfarin Pharmacogenetics Consortium (IWPC) were determined. This prospective study was approved by the Institutional Review Board of the General Hospital of Chinese People's Liberation Army, and informed consent was obtained from each patient.

Results The constructed pharmacogenetic refinement algorithms could explain 52.1% of the warfarin dose variability (R^2) in the derivation cohort. In the validation cohort, warfarin dose prediction was significantly more accurate with the pharmacogenetic refinement algorithm ($R^2=45.1\%$, mean absolute error (MAE): 0.65 ± 0.51 mg/day) than with the clinical algorithm ($R^2=25.6\%$, MAE: 0.75 ± 0.61 mg/day, $p=0.009$) and the IWPC algorithm ($R^2=27.7\%$, MAE: 0.81 ± 0.53 mg/day, $p=0.001$). When analysed in the subgroups, the pharmacogenetic refinement algorithm showed the best predictive accuracy of warfarin dose in patients with low dose requirement (<2.25 mg/day), patients who carried at least one of the genetic variants (CYP2C9*3, VKORC1 -1639 A/G, or CYP4F2 rs2108622 TT) and patients under low intensity anticoagulation (target INR 1.6–2.5).

Conclusions Pharmacogenetic refinement algorithm integrating early INR values, clinical factors and genotypes has the potential to improve the accuracy of warfarin dose estimation in Chinese patients.